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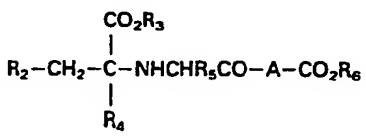
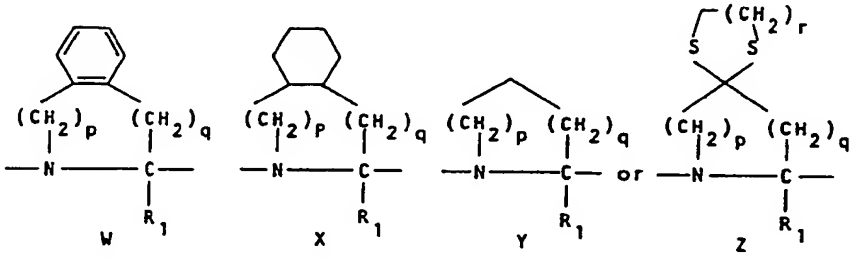
(54) Pharmaceutical composition.

(57) Topical ophthalmologically acceptable composition useful for reducing and controlling the elevated intraocular pressure associated with glaucoma which comprises an angiotensin converting enzyme (ACE) inhibitor in combination with an ophthalmologically acceptable carrier. Preferred compositions contain captopril or an ACE inhibitor of formula



I

wherein A is



W X Y Z

R_2 is alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1, R_3, R_4 and R_6 are hydrogen or alkyl;

R_5 is hydrogen, alkyl or amino alkyl;

p is o, 1 or 2;
q is 0, 1 or 2, provided that the sum of p and q is 1 or 2 and that p is not 0 in formula Z;
r is 1 or 2.

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PHARMACEUTICAL COMPOSITION

Glaucoma is an ocular disease complex associated with an elevated pressure within the eye (i.e., intraocular pressure, IOP). As a result of the elevated IOP, damage to the optic nerve head resulting in irreversible loss of visual function may ensue. Untreated, this condition may eventually lead to blindness.

Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field loss, is now believed by the majority of ophthalmologists to represent the earliest phase in the onset of glaucoma.

A number of the drugs presently employed to treat glaucoma are not entirely satisfactory, particularly in the earliest course of the disease when the side effects they produce are often worse than the symptoms of the disease.

Epinephrine used as a topical solution, must be utilized cautiously in patients with high blood pressure, diabetes, hyperthyroidism and cerebral artereosclerosis due to the possibility of systemic action.

Timolol, a clinically utilized, topically applied agent for lowering intraocular pressure, must be used with caution in patients in whom beta-adrenergic blockade may be undesirable. Systemic absorption of topically administered timolol and systemic beta-blockade are responsible for the contraindication of timolol therapy for gluacoma in patients with compromised pulmonary function.

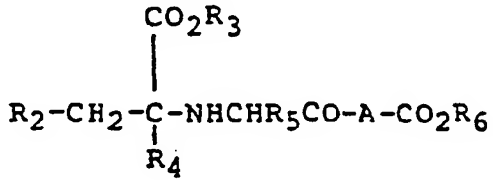
Pilocarpine, a topical drug, although considered systemically harmless and quite effective, may cause considerable local difficulties. Pupil constriction may cause the eye to lose its ability to adapt from light to dark. Accomodation may become stimulated so that the patient's refraction is sometimes incorrect and vision becomes blurred. The drug itself may cause a local vasodilation and red eyes. Irritation is common.

Carbonic anhydrase inhibitors have been used systemically but they have a number of disadvantages. While effective in lowering intraocular pressure, they often cause a numbness and tingling, gastrointestinal upsets and, frequently, depression, lethargy, a loss of appetite, and general malaise. European Patent Application 81400326.5, Publication number 36,351 attempts to overcome these difficulties by the topical administration of an alkali metal salt of a carbonic anhydrase inhibitor.

The presnet invention provides a pharmaceutical composition for reducing and controlling the elevated intraocular pressure associated with glaucoma.

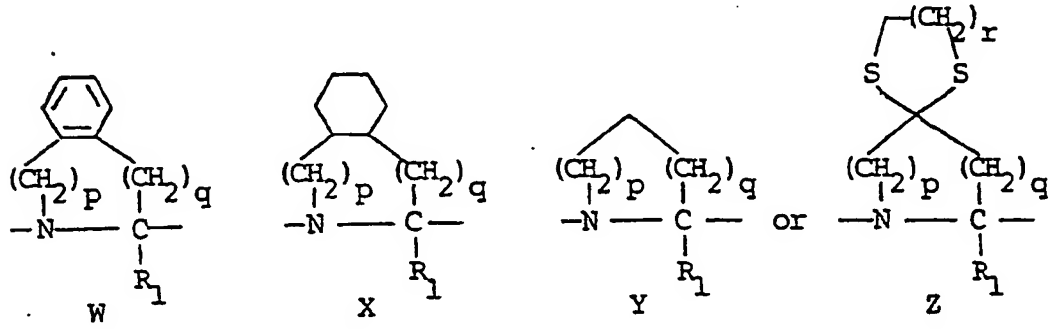
The invention sought to be patented in its pharmaceutical composition aspect is a topical ophthalmologically acceptable composition useful for reducing and controlling the elevated intraocular pressure associated with glaucoma which comprises an intraocular pressure reducing effective amount of a pharmaceutically acceptable angiotensin converting enzyme (ACE) inhibitor in combination with an ophthalmologically acceptable carrier for topical use. The composition may contain one or more additional therapeutic agents.

In a preferred composition according to this invention said ACE inhibitor is a compound having the structural formula



I

wherein A is



W X Y or Z

R_2 is alkyl having from 1 to 6 carbon atoms, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1, R_3, R_4, and R_6 are the same or different and are hydrogen or alkyl having from 1 to 6 carbon atoms;

R_5 is hydrogen, alkyl having from 1 to 6 carbon atoms or amino alkyl having from 1 to 6 carbon atoms;

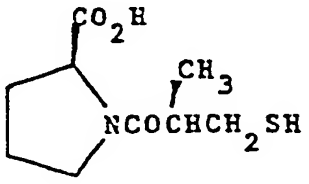
p is 0, 1 or 2;

q is 0, 1 or 2, provided that the sum of p and q is 1 or 2 and that p is not 0 in formula Z;

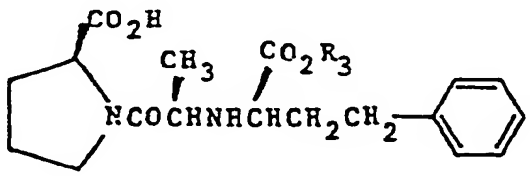
r is 1 or 2; and the pharmaceutically acceptable salts thereof.

Preferably in formula I R_1 and/or R_4 and/or R_6 is hydrogen and/or R_2 is benzyl and/or R_5 is methyl and/or p and/or q and/or r are 1. Preferably A is the group X, Y or Z. Preferably the compounds are of the S,S,S-configuration.

Preferred compositions of the invention comprise ACE inhibitors having the following structural formulae:



II



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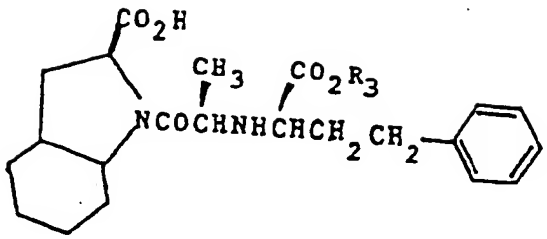
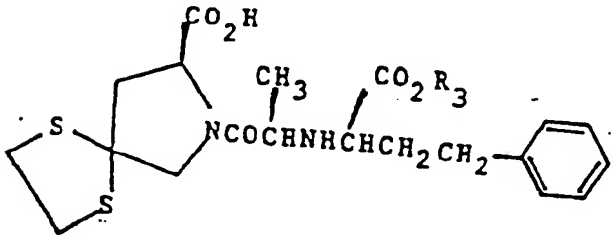


IV



V

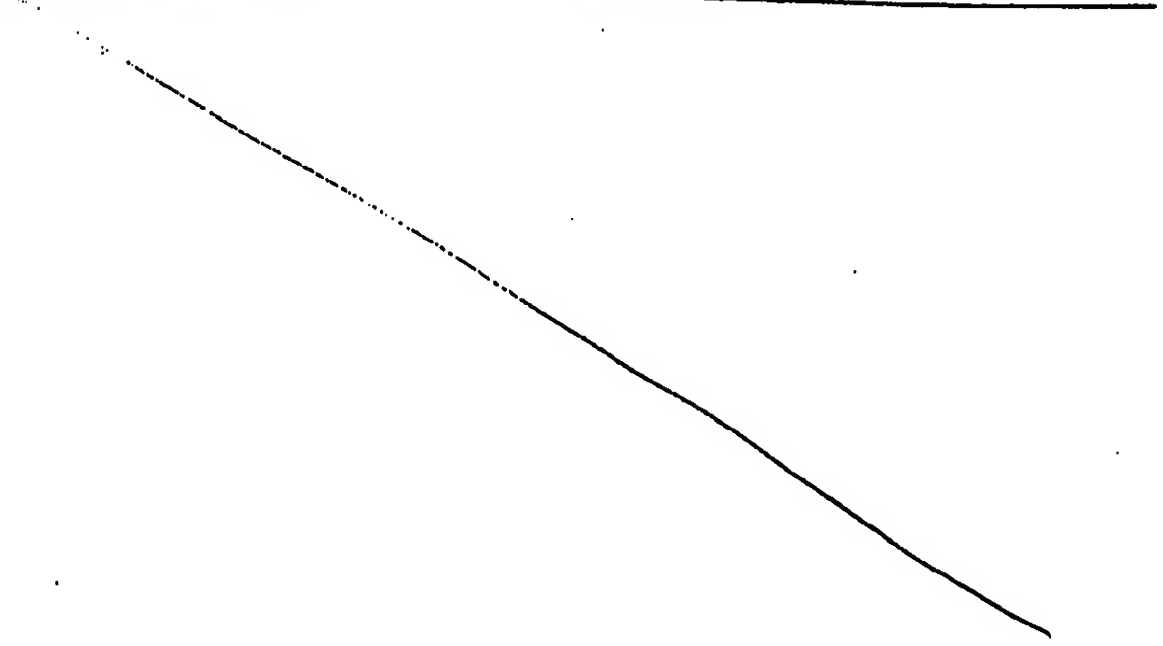
In the above formulae the heavy line (━) utilized at the chiral centers means that the substituent so bonded is projected above the plane of the paper. The configuration at these chiral centers is denoted as "S". The substituent R_3 may be hydrogen or alkyl having from 1 to 6 carbon atoms. R_3 is preferrably hydrogen or ethyl.

The invention sought to be patented in its pharmaceutical method aspect is a method for reducing and controlling the elevated intraocular pressure associatd with glaucoma in a human which method comprises administering to said human an effective amount of the above-defined pharmaceutical composition.

The compounds utilized in the topical ophthalmologically acceptable pharmaceutical compositions and methods of the invention are known in the art as angiotensin converting enzyme (ACE) inhibitors. Angiotensin II, a pressor substance, is produced in vivo by the action of angiotensin converting enzyme (ACE) on angiotensin I. Compounds capable of inhibiting the action of ACE are clinically useful for controlling the blood pressure of humans suffering from hypertension. For example, captopril, Compound II is currently in clinical use for this purpose. Other ACE inhibitors are known in the art, and may have a variety of structures. See, for example, An. Rev. Biochem., 51, 283(1982) and references cited therein.

described by Cushman and Cheung, Biochem. Pharmacol., 20, 1637(1971). The ACE used is prepared in a manner similar to that of Cheung and Cushman, Biochem. Biophys. Acta., 293, 451(1973). Incubation for ACE assays is carried out at 37°C. Each 0.25 ml assay mixture contains the following components: 100 mM of potassium phosphate buffer containing 300 mM sodium chloride, 5 mM HHL and 1.87 mU enzyme at pH 8.3 and various concentrations of inhibitors. The enzyme reaction is terminated after 60 minutes by the addition of 0.25 ml of 1N HCl. Inhibitors are dissolved in appropriate solvents. Hippuric acid solution for a standard curve is prepared in a similar manner.

Each experiment involves replicate incubations for each condition to be studied. IC_{50} values (the concentration required for the 50% inhibition of ACE activity) are derived from calculated regression lines. Each experiment utilizes multiple concentrations of inhibitor.



Many ACE inhibitors are known in the art and may be prepared by known methods or by variations thereof. For example, the compound having structural formula II may be prepared as described in United States Patent 4,046,889; the compounds having structural formulae III and IV may be prepared as described in European Patent Application 81108348.4, publication number 50,800.

The compositions of this invention are considered to be no more toxic than compositions containing the ACE inhibitors for controlling hypertension.

When topically administered to the eye, the compounds of the invention reduce intraocular pressure (IOP). For example, compound II caused falls in IOP of a magnitude similar to those produced by the anti-glaucoma agent timolol when each were administered at concentrations of 0.25, 0.5, 1.0 and 2.0 (w/v%) and tested by the following procedure:

Male New Zealand white rabbits having a normal IOP are conditioned to the laboratory setting for at least one 4 hr period before being used to study drug effects. A Makay-Marg applanation tonometer is used to measure IOP. Readings, in mm Hg, are taken in triplicate and the average is recorded.

Rabbits are restrained in a cloth sack 2 min. prior to IOP determination. The left lower eyelid is retracted to form a pouch and 1 drop of a local anesthetic is irrigated over the cornea. The lower eyelid is then held closed over the eye for about 1 min. Corneal anesthesia is repeated before each set of IOP determinations. Readings are taken just before dosing with drug (0 time) and at hourly intervals thereafter. Drugs are administered in a 50 ul volume in the same manner as the anesthetic.

Summary of test results:

observation time : 4 hours

pretreatment intraocular pressure: 19.6-21.4 mmHg

compound	concentration %	maximum decrease [mmHg]
Timolol	0.25	-1.7 ± 0.6
	0.5	-2.4 ± 0.8
	1.0	-4.4 ± 0.4
	2.0	-3.6 ± 0.7
Captopril	0.25	-2.4 ± 0.5
	0.5	-2.4 ± 0.8
	1.0	-3.7 ± 0.6
	2.0	-4.1 ± 0.6
I	0.1	-3.7 ± 0.9
	0.25	-2.1 ± 0.7
	0.5	-3.4 ± 1.1
	1.0	-3.2 ± 0.7
II	0.25	-3.5 ± 0.6
	0.5	-1.2 ± 0.7
	1.0	-2.7 ± 1.1

I: N-[1-(S)-Carboxy-3-phenylpropyl]-(S)-alanyl-(S)-proline

II: 1-{N-[1(S)-Carboxy-3-phenylpropyl]-(S)-alanyl}-cis,syn-octahydroindole-2(S)-carboxylic acid

The active compounds of the invention (ACE inhibitors) are administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye; such as solutions, suspensions, ointments and solid inserts. Formulations of these compounds may contain from 0.01 to 5% and especially 0.25% to 2% of medicament. Other concentrations may be employed provided the dose is effective in lowering intraocular pressure. As a unit dosage form, between 0.01 to 2.5 mg., preferably 0.05 to 2.5 mg., and especially 0.1 to 1.0 mg. of the active compound is applied to the human eye, generally on a daily basis. Individual dosage requirements are variable; however, and must be administered on the basis of the severity of the disease and the response of the patient.

To prepare suitable dosage forms, the active compounds may be conveniently admixed with a non-toxic pharmaceutically acceptable carrier suitable for topical ophthalmolgic administration. Typical of such pharmaceutically acceptable carriers are, for example, water, mixtures of water and watermiscible solvents such as lower alkanols or vegetable oils, petroleum based jelly, and including also from 0.5 to 5% by weight of hyroxyethyl cellulose, ethyl oleate, carboxymethyl cellulose, polyvinylpyrrolidone, and other water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose, alkali metal carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose; acrylates such as polyacrylic acids salts, ethylacrylates; polyacrylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as

thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol; buffering ingredients such as alkali metal chloride, borate, acetate, gluconate buffers; antioxidants such as sodium metabisulfite, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and the like; and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl alkali metal sulfosuccinate, monothioglycerol, ethylenediamine tetracetic acid and the like.

Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic alkali chloride vehicles, tris and the like.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Inserts that are known in the art that are suitable for this use include those described in British

Patent 15611, and in United States Patents 3,993,071; 3,986,510; 3,868,445; and 3,867,510. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The compositions of the invention may include additional therapeutic agents in addition to the ACE inhibitor. For example antibiotics, anesthetics as well as other IOP lowering agents may be present.

In the following formulation examples A and B stand for the active ingredients:

A: 1-{N-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl}-cis,syn-octahydroindole-2(S)-carboxylic acid

B: 7-{N-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl}-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

*stands for the concentration of the active ingredient which is as follows:

	active ingredient A	active ingredient B	
Example 1	10	8	[mg/ml]
Example 2	12	18	[mg/ml]
Example 3	20	15	[mg/g]
Example 4	15	25	[mg/g]
Example 5	5		[mg/ml]

The formulations are prepared by standard procedures.

Ophthalmic Solutions:

Example 1	mg/ml
active ingredient A or B	*
Polyvinyl Alcohol	20.0
Sodium phosphate Dibasic	1.2
Sodium phosphate Monobasic	0.64
Edetate Disodium	0.1
Sodium Chloride	6.0
Benzalkonium Chloride	0.1
Purified Distilled Water QS. A.D.	1.0ml

Example 2	mg/ml
active ingredient A or B	*
Hydroxypropyl Methylcellulose	5.0
Boric acid	10.0
Benzalkonium Chloride	0.1
Sodium Borate	0.7
Edetate Disodium	0.1
Sodium Chloride	3.0
Purified Distilled Water QS.A.D.	1.0ml

Ophthalmic Ointment:

Example 3	Mg/g.
active ingredient A or B	*
Purified Distilled Water	0.1ml
Methyl Paraben	0.8
Propyl Paraben	0.1
Hydrophilic Petrolatum QS. A.D.	1.0g

Example 4	Mg/g.
active ingredient A or B	*
Chlorobutanol	5
Anhydous lanolin	10
Mineral Oil	10
White Petrolatum QS. A.D.	1.0g

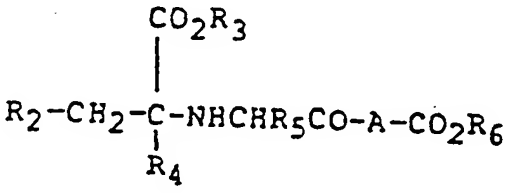
Opthalmic jel:

Example 5	Mg/g.
active ingredient A or B	*
Hydroxypropyl Methylcellulose	40.0
Boric Acid	10.0
Benzalkonium Chloride	0.1
Sodium Borate	0.7
Edetate Disodium	0.1
Purified Distilled Water QS. A.D.	1.0ml

CLAIMS for designated countries other than Austria

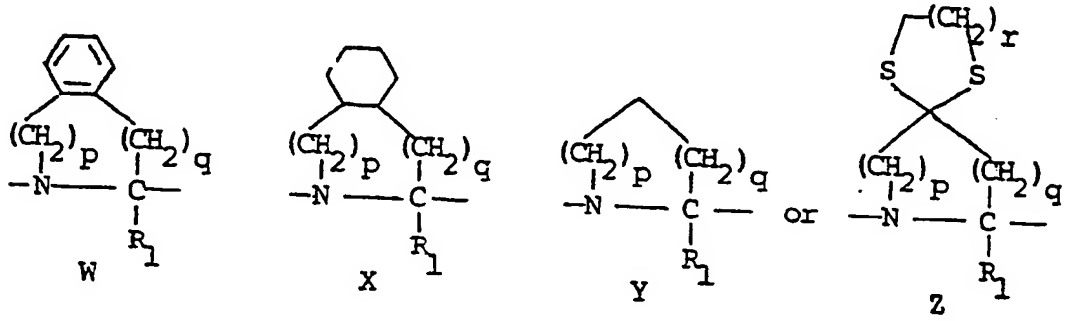
1. A topical ophthalmologically acceptable composition for reducing and controlling the elevated intraocular pressure associated with glaucoma which comprises an intraocular pressure reducing effective amount of a pharmaceutically acceptable angiotensin converting enzyme inhibitor, in combination with an ophthalmologically acceptable carrier for topical use.

2. The composition defined in claim 1 wherein said ACE inhibitor is a compound having the structural formula



I

wherein A is



R_2 is alkyl having from 1 to 6 carbon atoms, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1, R_3, R_4, and R_6 are the same or different and are hydrogen or alkyl having from 1 to 6 carbon atoms;

R_5 is hydrogen, alkyl having from 1 to 6 carbon atoms or amino alkyl having from 1 to 6 carbon atoms;

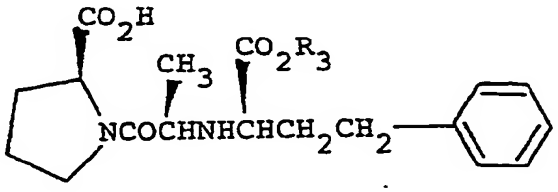
p is 0, 1 or 2;
q is 0, 1 or 2, provided that the sum of p and q is 1 or 2 and that p is not 0 in formula Z;
r is 1 or 2; and the pharmaceutically acceptable salts thereof.

3. The composition of claim 2, wherein in formula I R_1 and/or R_4 and/or R_6 is hydrogen and/or R_2 is benzyl and/or R_5 is methyl.

4. The composition of claim 2 or 3, wherein in formula I p and/or q and/or r is 1.

5. The composition of any one of claims 2 to 4 wherein in formula I A is the group X, Y or Z.

6. The composition of any one of claims 2 to 5, wherein said ACE inhibitor is



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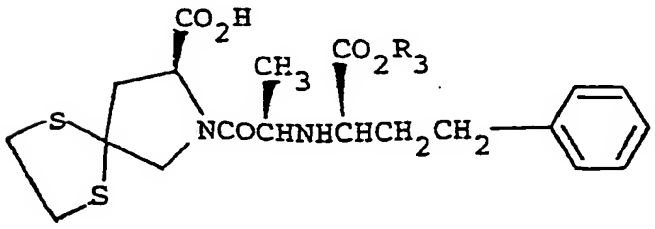

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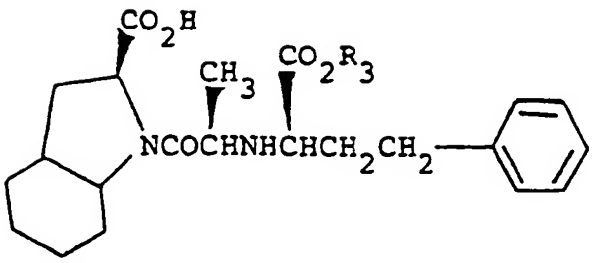
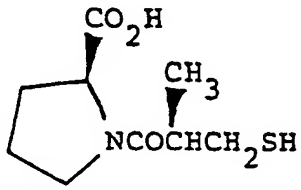


7. The composition according to any one of claims 2 to 6, wherein R_3 is hydrogen or ethyl.

8. The composition defined in claim 1, wherein said ACE inhibitor is



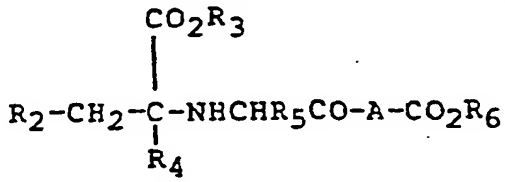
9. Composition as defined in any one of claims 1 to 8 in the form of a dosage unit.

10. Use of a composition as defined in any one of claims 1 to 9 for reducing and controlling the elevated intraocular pressure associated with glaucoma.

CLAIMS for Austria

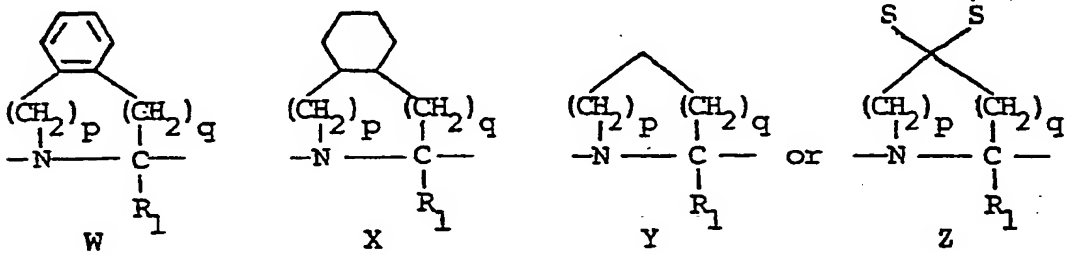
1. Process for the preparation of a topical ophthalmologically acceptable composition for reducing and controlling the elevated intraocular pressure associated with glaucoma, characterized in that an intraocular pressure reducing effective amount of a pharmaceutically acceptable angiotensin converting enzyme inhibitor is admixed with an ophthalmologically acceptable carrier for topical use.

2. Process according to claim 1, characterized in that said ACE inhibitor is a compound having the structural formula



I

wherein A is



W X Y or Z

R_2 is alkyl having from 1 to 6 carbon atoms, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1, R_3, R_4, and R_6 are the same or different and are hydrogen or alkyl having from 1 to 6 carbon atoms;

R_5 is hydrogen, alkyl having from 1 to 6 carbon atoms or amino alkyl having from 1 to 6 carbon atoms;

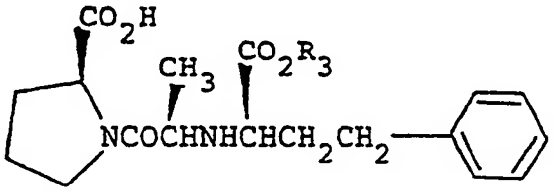
p is 0, 1 or 2;
q is 0, 1 or 2, provided that the sum of p and q is 1 or 2 and that p is not 0 in formula Z;
r is 1 or 2; and the pharmaceutically acceptable salts and thereof.

3. Process according to claim 1, characterized in that in formula I R_1 and/or R_4 and/or R_6 is hydrogen and/or R_2 is benzyl and/or R_5 is methyl.

4. Process according to claim 2 or 3, characterized in that in formula I p and/or q and/or r is 1.

5. Process according to any one of claims 2 to 4, characterized in that in formula I A is the group X, Y or Z.

6. Process according to any one of claims 2 to 5, characterized in that said ACE inhibitor is



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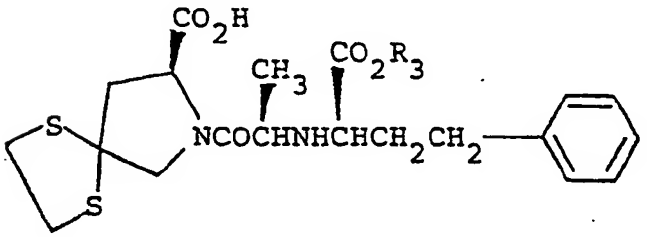

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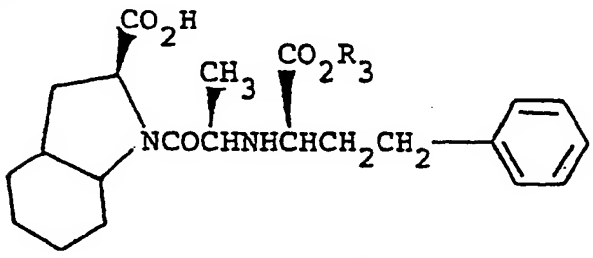

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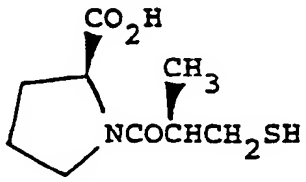
7. Process according to any one of claims 2 to 6, characterized in that R_3 is hydrogen or ethyl.

8. Process according to claim 1, characterized in that said ACE inhibitor is



9. Process according to any one of claims 1 to 8, characterized in that the composition is brought into the form of a dosage unit.